Remarks

Claims 50-92 are pending in the application following entry of this Amendment. Claims 23-41, 43-45, and 47-49 have been canceled. Claims 59-92 have been added. Claims 50 and 54 have been amended.

In view of elections previously required by the Examiners, claims 55-58, 64-66, 69-75, 81-83, and 86-92 stand withdrawn from consideration pending rejoinder.

Claims 50 and 54 are the only independent claims pending. Claims 51-53 and 56-75 depend from claim 50. Claims 55 and 76-92 depend from claim 54.

In the Office Action, the Examiner did not acknowledge that claims 56-58 had been added in the Supplemental Amendment filed by the Applicants on 15 July 2004. The Examiner also did not refuse to enter claims 56-58. The Applicants believe that this was merely an oversight, and ask that the Examiner confirm that claims 56-58 are currently pending. If claims 56-58 were not previously added, then please consider them added herein.

No new matter is added by the amendments and additions made herein. Support for the amendments to the claims is found in the specification as follows.

In claims 50 and 54, the Markush group listing potential identities for moieties R^1 (in claim 50) and R^4 (in claim 54) has been expanded to include the list of moieties disclosed in the specification at page 6, lines 21-23.

Canceled claims 24-41, 43-45, and 47-49, which previously depended from canceled independent claim 23 have been duplicated as i) claims 59-75, which depend from independent claim 50 and ii) claims 76-92, which depend from independent claim 54. For the Examiner's convenience, the following table indicates the canceled claims to which the newly added claims correspond.

Claim Correspondence

Old Claim #	New Claim #s	Old Claim #	New Claim #s	Old Claim #	New Claim #s
24	59, 76	33	61, 78	42	-
25	60, 77	34	62, 79	43	70, 87
26	-	35	63, 80	44	71, 88
27	-	36	64, 81	45	72, 89
28	-	37	65, 82	46	-
29	-	38	66, 83	47	73, 90
30	-	39	67, 84	48	74, 91
31	-	40	68, 85	49	75, 92
32	-	41	69, 86		

Compliance with Previous Restriction/Election Requirements

In the restriction / election requirement issued 16 July 2002 (Paper No. 2), the Examiner required election of a single species of enzyme. The enzyme species, 'phosphatase' was elected. Claims 50-54, 59-68, and 76-85 read on this elected species.

In the restriction / election requirement issued 16 July 2002 (Paper No. 2), the Examiner required election of a single species of 'targeting molecule.' The targeting molecule species, 'antibody' was elected. Claims 50-92 read on this elected species.

In the restriction / election requirement issued 16 July 2002 (Paper No. 2), the Examiner required election of a single species of R^1 moiety. The R1 moiety species, 'gamma emitter' was elected. Claims 50-63, 67-80, and 84-92 read on this elected species.

In the restriction / election requirement issued 16 July 2002 (Paper No. 2), the Examiner required election of a single species of 'BLOCK' (roughly corresponding to the "prosthetic group" recited in the presently pending claims). The BLOCK species 'phosphoric acid or sulfuric acid' was elected. Claims 50-54, 59-68, and 76-85 read on this elected species.

In the restriction / election requirement issued 28 October 2002 (Paper No. 4), the Examiner required election of a single species of either 'endogenous enzyme' or 'gene therapy

induced enzyme.' The species 'endogenous enzyme' was elected. Each of claims 50-92 reads on the elected species.

In view of the restriction / election requirements and the elected species, each of claims 50-54, 59-63, 67, 68, 76-80, 84, and 85 read on all elected species. Claims 55-58, 64-66, 69-75, 81-83, and 86-92 stand withdrawn from consideration, are believed to be subordinate to generic linking claims, and are maintained pending possible rejoinder. The Applicant believes that each of claims 50-54, 59-63, 67, 68, 76-80, 84, and 85 should be examined on the merits, and that each of claims 55-58, 64-66, 69-75, 81-83, and 86-92 should be rejoined and examined on the merits in the event the corresponding linking claim is found to be allowable in view of the elected species.

Each of the Examiner's objections or rejections is addressed below in the order they were presented in the Office Action dated 21 October 2004.

Rejection Pursuant to 35 U.S.C. § 112

On page 3 of the Office Action, the Examiner rejects claim 54 pursuant to 35 U.S.C. § 112, first paragraph. In the Examiner's opinion, the specification does not disclose prosthetic groups, other than beta-D-galactosyl moieties which can be attached to the indolyl moiety recited in claim 54. The Examiner recognizes that the specification discloses (e.g., on the lower half of page 14) a class of beta-D-galactose-substituted indole compounds.

The Applicants respectfully contend that the Examiner has not adequately considered the breadth of the Applicants' disclosure in view of what was known in the art at the time the invention was made. On page 6, lines 11-23 of the specification, the Applicants disclose that the blocking group can be any moiety that can be cleaved from the remainder of the prodrug substrate by action of an enzyme. The Examiner is correct that the ability of beta-galactosidase to cleave beta-D-galactosyl moieties from indolyl-3-beta-D-galactosyl moieties (as exemplified on page 14 of the specification) was known at the time the invention was made. However, the Examiner appears to believe that beta-D-galactosyl moieties were the only moieties known at that time to be enzymatically cleavable from indole compounds. This is not accurate. As the

enclosed article of Smejkal et al. demonstrates (see first page, left column, first paragraph, references to articles by Kim and Wyckoff and by Haugland), use of substituted indolyl-3-phosphates as a substrate for phosphatases was well known by at least 1999. Furthermore, the enclosed PubMed citations to older articles by Horwitz et al. and by Tsou et al. demonstrate that substituted indolyl-3-phosphate and -sulfate compounds were well known substrates of phosphatases and sulfatases.

The Applicants respectfully contend that, as of the time the Applicants made the present invention, indolyl moieties were widely recognized in the art as components of compounds from which enzyme-specific moieties (e.g., phosphate, sulfate, and galactosyl moieties) could be cleaved. The Applicants believe that the general description of suitable compounds that appears on page 6 of the specification, taken together with the specific example of an indolyl-3-galactosyl compound on page 14 of the specification and the knowledge of skilled artisans at the time the invention was made, sufficiently describes to a skilled artisan the full range of compounds encompassed by claim 54.

The Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claim 54 pursuant to 35 U.S.C. § 112, first paragraph.

Rejections Pursuant to 35 U.S.C. § 102

On pages 3 and 4 of the Office Action, the Examiner rejects claims 23-25, 33, and 40 pursuant to 35 U.S.C. § 102(e) over Pero. Each of claims 23-25, 33, and 40 has been canceled, and the Applicants believe that this rejection is moot for that reason.

On pages 5 and 6 of the Office Action, the Examiner rejects claims 23-28, 31-33, and 40 pursuant to 35 U.S.C. § 102(b) over Senter. Each of claims 23-28, 31-33, and 40 has been canceled, and the Applicants believe that this rejection is moot for that reason.

Rejection of Claims Including Claims 50-53 Pursuant to 35 U.S.C. § 103(a)

On pages 6-9 of the Office Action, the Examiner rejects claims 23-28, 31-33, 40, and 50-53 pursuant to 35 U.S.C. § 103(a) over Pastan (USPN 5,489,525) in view of Haugland (USPN

5,316,906), Hansen (USPN 5,851,527), Lebioda (USPN 5,763,490), Mertens (USPN 5,021,220), and Christenson (USPN 4,107,1285). Each of claims 23-28, 31-33, and 40 has been canceled, and the rejection is believed to be moot with regard to those claims. The following comments pertain to claims 50-53 (and other pending and withdrawn claims which depend from claim 50).

Pastan teaches binding an antibody-coupled enzyme to a prostate tumor site and administering to the tumor-bearing animal a prodrug that is cleaved by the antibody-coupled enzyme to generate a more cytotoxic compound at the tumor site (e.g., col. 7, lines 44-68). Haugland discloses quinazolinone derivatives, including phosphorylated derivatives, and that such derivatives can be enzymatically cleaved to precipitate non-toxic quinazolinone compounds near a cell (e.g., col. 6, lines 55-58). Hansen discloses use of an antibody-coupled enzyme for cleavage of a soluble substrate-agent complex to deposit a less soluble agent at the site of antibody binding (e.g., see abstract and col. 3, lines 44-53). Lebioda appears to be cited merely for the proposition that prostatic acid phosphatase (PAP) is present in patients afflicted with prostate cancer (see col. 2, lines 11-14). Mertens appears to be cited because it discloses a method of generating radio-halogenated aromatic or heteroaromatic compounds. Christenson appears to be cited as an example of a standard method of radioiodinylating a quinazolinone compound.

In the Examiner's view, a skilled artisan could have radioiodinylated a quinazolinone compound of the type described by Haugland and precipitated it at the site of a prostate tumor by pre-treating the prostate tumor site with an enzyme-coupled antibody, as described by Pastan (or Hansen). The Examiner asserts that a skilled artisan would be motivated to construct an antibody coupled with a phosphatase enzyme such as PAP.

The Applicants respectfully contend that the Examiner has improperly used the Applicants' claims as a roadmap for performing a hindsight-based assembly of prior art. Nonetheless, in order to speed prosecution of claims that the Applicants believe the Examiner can most quickly find allowable, the Applicants have canceled independent claim 23 and the claims depending therefrom. Canceled independent claim 23 encompassed the enzyme-conjugated antibody-based methods that the Examiner contends are obvious. The Applicants reserve the right to pursue claims identical to or like claim 23 in a related application.

Pending independent claim 50 does not encompass an enzyme-conjugated antibody-based method. Instead, claim 50 recites that the enzyme which cleaves the prosthetic group from the prodrug recited in the claim is one that is present in the extracellular space of the tumor and is produced naturally by cells of the tumor. Although the quinazolinone compounds recited in claim 50 may have been described by others (e.g., Haugland) and incorporation of a radionuclide into such compounds may have been within the skill of an ordinary artisan, there is no teaching or suggestion that such compounds (whether radiolabeled or not) could be administered to a patient bearing a tumor or that such compounds would be localized within the tumor. To the contrary, Haugland teaches use of these compounds only in *in vitro* (histochemical analysis) applications. The methods disclosed in Pastan and Hansen rely on use of an antibody-linked enzyme for localization of an anti-tumor agent at the tumor site. Lebioda discloses that PAP is secreted "throughout the body" (col. 1, lines 66-67) in prostate cancer patients, providing no motivation for a skilled artisan to believe that the quinazolinone compounds recited in claim 50 would be selectively localized within a solid (prostate) tumor, as recited in claim 50, in prostate cancer patients.

The Applicants respectfully contend that by amending claim 50 to exclude enzyme-conjugated antibody-based methods of the type disclosed in Pastan and Hansen, claim 50 has been clearly distinguished from the prior art. The Examiner is respectfully requested to reconsider and withdraw the rejection pursuant to 35 U.S.C. § 103(a) as applied to claims 50-53.

Rejection of Claims Including Claim 54 Pursuant to 35 U.S.C. § 103(a)

On pages 9 and 10 of the Office Action, the Examiner rejects claims 23-28, 31-33, 40, and 54 pursuant to 35 U.S.C. § 103(a) over Pastan in view of Haugland (1995 catalog reference), Haugland (USPN 5,316,906), Hansen, Lebioda, Mertens, and Rose (USPN 5,816,259). Each of claims 23-28, 31-33, and 40 has been canceled, and the rejection is believed to be moot with regard to those claims. The following comments pertain to claim 54 (and other pending and withdrawn claims which depend from claim 54).

Pastan, Haugland (USPN 5,316,906), Hansen, Lebioda, and Mertens were summarized above. Haugland (1995 catalog reference) appears to be cited merely for the proposition that

indolyl-phosphates can be cleaved by a phosphatase to yield a substantially insoluble indole compound. Rose discloses that radio-labeled indolyl-phosphate compounds can be conjugated with an antigen-binding agent (e.g., an antibody), bound to cells, endocytosed, cleaved from the agent, and exert a cytotoxic effect within the cell.

In the Examiner's view, a skilled artisan could have radioiodinylated an indolyl compound of the type described by Haugland (1995 catalog reference) and precipitated it at the site of a prostate tumor by pre-treating the prostate tumor site with an enzyme-coupled antibody, as described by Pastan (or Hansen). The Examiner asserts that a skilled artisan would be motivated to construct an antibody coupled with a phosphatase enzyme such as PAP.

As with the obviousness rejection applied to claims 50-53, the Applicants respectfully contend that the Examiner has improperly used the Applicants' claims as a roadmap for performing a hindsight-based assembly of prior art. Nonetheless, in order to speed prosecution of claims that the Applicants believe the Examiner can most quickly find allowable, the Applicants have canceled independent claim 23 and the claims depending therefrom.

Pending independent claim 54 does not encompass an enzyme-conjugated antibody-based method. Instead, claim 54 recites that the enzyme which cleaves the prosthetic group from the prodrug recited in the claim is one that is present in the extracellular space of the tumor and is produced naturally by cells of the tumor. Although the indolyl compounds recited in claim 54 may have been described by others (e.g., the Haugland catalog reference) and incorporation of a radionuclide into such compounds may have been within the skill of an ordinary artisan, there is no teaching or suggestion that such compounds (whether radiolabeled or not) could be administered to a patient bearing a tumor or that such compounds would be localized within the tumor. To the contrary, Haugland (1995 catalog reference) teaches use of these compounds only in *in vitro* (histochemical analysis) applications. The methods disclosed in Pastan and Hansen rely on use of an antibody-linked enzyme for localization of an anti-tumor agent at the tumor site. Lebioda discloses that PAP is secreted "throughout the body" (col. 1, lines 66-67) in prostate cancer patients, providing no motivation for a skilled artisan to believe that the indolyl compounds recited in claim 54 would be selectively localized within a solid (prostate) tumor, as recited in claim 54, in prostate cancer patients.

The Applicants respectfully contend that by amending claim 54 to exclude enzyme-conjugated antibody-based methods of the type disclosed in Pastan and Hansen, claim 54 has been clearly distinguished from the prior art. The Examiner is respectfully requested to reconsider and withdraw the rejection pursuant to 35 U.S.C. § 103(a) as applied to claims 54.

Summary

The Applicants respectfully contend that each of claims 50-54, 59-63, 67, 68, 76-80, 84, and 85 is in condition for allowance, and that claims 55-58, 64-66, 69-75, 81-83, and 86-92 should be rejoined and likewise found to be in condition for allowance. The Examiner is requested to issue a Notice of Allowance for each of claims 50-92 at the earliest possible time.

Respectfully submitted,

Amin I. KASSIS et al.

21 April 2005
(Date)

By: _____

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